ARTICLES

Cancer Risk After Iodine-131 Therapy for Hyperthyroidism

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Cancer incidence was studied in 10552 patients (mean age, 57 years) who received ^{131}I therapy (mean dose, 506 MBq) for hyperthyroidism between 1950 and 1975. Follow-up on these patients was continued for an average of 15 years. Record linkage with the Swedish Cancer Register for the period 1958-1985 identified 1543 cancers occurring 1 year or more after ^{131}I treatment, and the standardized incidence ratio (SIR) was 1.06 (95% confidence interval = 1.01-1.11). Significantly increased SIRS were observed for cancers of the lung (SIR = 1.32; n = 105) and kidney (SIR = 1.39; n = 66). Among 10-year survivors, significantly elevated risks were seen for cancers of the stomach (SIR = 1.33; n = 58), kidney (SIR = 1.51; n = 37), and brain (SIR = 1.63; n = 30). Only the risk for stomach cancer, however, increased over time (*P* <.05) and with increasing activity administered (*P* = not significant). The risk for malignant lymphoma was significantly below expectation (SIR = 0.53; n = 11). Overall cancer risk did not increase with administered ^{131}I dose or with time since exposure. The absence of any increase in leukemia adds further support to the view that a radiation dose delivered gradually over time is less carcinogenic than the same total dose received over a short time. Only for stomach cancer was a possible radiogenic excess suggested. [J Natl Cancer Inst 83:1072-1077, 1991]

Since its introduction in the 1940s, ^{131}I has been one of the most common therapies for hyperthyroidism. In many clinics, ^{131}I is the therapy of choice for both Graves' disease and toxic nodular goiter, largely because serious side effects are uncommon. There is still concern as to the possible carcinogenic effects of ^{131}I. Although several studies of patients treated with ^{131}I for hyperthyroidism have been conducted *(1-5)*, no clear pattern of increased cancer risks has been observed. Most noteworthy, leukemia has never been found to be in excess following ^{131}I therapy for hyperthyroidism. In a recent study *(6)*, the standardized rate ratio for breast cancer among women treated with ^{131}I for hyperthyroidism was 1.9 (95% confidence interval [CI] = 0.9-4.1) compared with those who did not receive ^{131}I. Helm *(5)* did not observe any increased risk for breast cancer in patients following ^{131}I therapy for hyperthyroidism, but found an elevated risk for brain tumors in women. The follow-up periods in most studies have been short.

The present study evaluates the risk for leukemia and solid tumors in a large series of Swedish patients treated for hyperthyroidism with known activities of ^{131}1.

Patients and Methods

All patients were recruited from seven hospital radiotherapy and oncology departments in Sweden (South Hospital and

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Radiumhemmet, Stockholm; University Hospital, Uppsala; Malmö General Hospital, Malmö; University Hospital, Lund; Sahlgren's Hospital, Gothenburg; and University Hospital, Umeå). Patients at one hospital (Radiumhemmet) had previously been studied *(5)*, and this series was extended to 9 additional years of follow-up.

A total of 10646 patients (82% women and 18% men) under the age of 75 were identified as having received ^{131}I therapy for hyperthyroidism between 1950 and 1975. Excluded from the study were 94 patients (0.9%) for whom we had insufficient information on names and dates of birth. The cohort was composed of 10552 patients. Three percent of the patients had previously been treated with external radiotherapy to the head and neck region for various reasons. Two percent had previously received thyroid hormone supplements for treatment of a nontoxic goiter, and 3% had had surgery for the same reason. Nearly 24% had received antithyroid drugs at some time prior to their ^{131}I therapy, and 14% had had previous surgery for hyperthyroidism.

The mean age of the patients at the time of the first ^{131}I treatment was 57 years overall (range, 13-74 years), 56 years for men and 57 years for women. Six percent of the patients were under 40 years of age. Twenty-one percent of the patients were treated in the 1950s, 46% in the 1960s, and 33% in the 1970s.

Information on thyroid disease and treatment was abstracted from the patients' records, which usually distinguished between Graves' disease (51%) and toxic nodular goiter (42%). The latter category included both thyroid glands with solitary nodules and multinodular goiter. Information on the type of disease was not available for 7% of the patients.

Fifty-nine percent of the patients received one treatment, 27% received two treatments, and 14% received three or more treatments. The mean total activity administered was 506 MBq (1 mCi = 37 MBq), 360 MBq to patients with Graves' disease and 700 MBq to those with toxic nodular goiter. A total activity of 220 MBq or less (mean, 150 MBq) was given to 30% of the patients, 221-480 MBq (mean, 315 MBq) to 38%, and more than 480 MBq (mean, 1063 MBq) to 32%.

The International Commission on Radiological Protection tables *(7)* and data from Edmonds and Smith *(8)* were used to estimate the radiation dose from ^{131}I treatment to various organs. The dose to the thyroid was aimed at 60-100 Gy per treatment and was sufficient to kill substantial numbers of thyroid cells. Doses to organs other than the thyroid were relatively low. An average dose of less than 10 cGy was estimated for the colon, liver, pancreas, lungs, breast, uterus, ovaries, testis, kidneys, and bone marrow. The dose to the bladder was 14 cGy, to the salivary glands 20 cGy, and to the stomach about 25 cGy. The effective half-life of ^{131}I (about 6 days) gives a protracted exposure, with nearly 95% of the dose being delivered in 4 weeks.

The roster of patients with hyperthyroidism was linked to the Swedish Cancer Register (SCR) for the period 1958-1985. The SCR was established in 1958 and collects nationwide notifications of newly diagnosed cancers. Matches were determined based on the unique 10-digit identification number given to each individual in Sweden.

Record linkage with the Swedish Cause of Death Register, which was started in 1952, identified 172 deaths before 1958 among the 1690 patients included prior to that year. None of these deaths were due to leukemia.

All patients were considered to be at risk from 1 year after the initial ^{131}I treatment or from 1958 if first treatment occurred prior to that year. The period at risk lasted until death or until December 31, 1985. In the calculation of person-years at risk, the 1st year was excluded for each individual first treated in 1958 or later. All cancers observed within the 1st year after treatment and cancers reported prior to treatment were also excluded.

The expected numbers of malignant tumors were calculated by indirect standardization. Adjustment was made for age, sex, region of residence, and calendar year-specific cancer incidence data for the whole country obtained from the SCR for the period 1958-1985.

The standardized incidence ratio (SIR) was calculated as the ratio of observed-to-expected numbers of cancers. The 95% CI was determined by assuming the observed numbers of cases to be distributed as a Poisson variable. In comparisons of SIRS among different exposure groups, chi-square statistics were used.

Results

Within the 1st year of follow-up, 345 patients died and the analyses were thus based on 10207 patients. The person-years at risk were 139018 (23457 among men and 115561 among women). The mean follow-up time of patients who survived longer than 1 year was 15 years after treatment with a maximum of 28 years.

A total of 1543 cancers were observed in the cohort more than 1 year after the first ^{131}I treatment (SIR = 1.06; 95% CI = 1.01-1.11; Table 1). Forty-six percent of the reported cases ap-

Table 1. Observed No. of cancers and SIR with 95% CI in patients treated with ^{131}I for hyperthyroidism 1 year or more after therapy

Cancer site or type	Average organ dose, cGy	No. of cancers	SIR	95% CI
Oral cavity, pharynx	7	21	1.02	0.63-1.55
Salivary glands	20	3	0.84	0.18-2.43
Stomach	25	92	1.05	0.85-1.28
Liver	5	23	1.33	0.84-1.99
Pancreas	5	63	1.12	0.86-1.43
Colon, rectum	5	209	1.10	0.95-1.25
Lung	7	105	1.32	1.07-1.59
Female breast	6	269	1.02	0.90-1.15
Female genital organs	5	182	1.00	0.85-1.15
Male genital organs	5	77	1.00	0.79-1.25
Kidney	5	66	1.39	1.07-1.76
Bladder	14	51	1.12	0.84-1.47
Brain	*	48	1.30	0.96-1.72
Thyroid gland	>10 000	18	1.29	0.76-2.03
Parathyroid gland	*	30	1.78	1.20-2.54
Lymphomas	6	28	0.72	0.48-1.03
Hodgkin's disease		6	0.83	0.31-1.81
Non-Hodgkin's lymphomas		22	0.68	0.43-1.04
Multiple myeloma	6	21	1.05	0.65-1.60
Leukemias	6	34	0.94	0.65-1.31
All cancer sites and types†	*	1543	1.06	1.01-1.11

*No estimate.
†Includes sites and cancer types not listed in table.

peared 1-9 years after treatment, and 54% were reported 10 years after therapy or later. There were 315 cases among men (SIR = 1.03; 95% CI = 0.92-1.15) and 1228 cases among women (SIR = 1.07; 95% CI = 1.01-1.13). There was no statistically significant difference in SIRS between patients less than 50 years old and those 50 years old or older.

Cancers of the lung and kidney and tumors of the parathyroid gland occurred significantly above expectation (Table 1). The risk for thyroid cancer was above expectation, and the risks for cancer of the salivary glands, lymphomas, and leukemias were below expectation, although none of the SIRS differed significantly from unity.

Patients with Graves' disease had a slightly lower overall cancer risk (SIR = 0.99) than patients with toxic nodular goiter (SIR = 1.12; Table 2). None of the site-specific SIRS among patients with Graves' disease differed from unity, whereas in patients with toxic nodular goiter, cancers of the lung, liver, and brain were significantly elevated.

Overall cancer risk was slightly elevated after 10 or more years of follow-up (SIR = 1.10; Table 3); there was, however, little variation in risk over time since treatment (Table 4). Among 10-year survivors, cancers of the stomach, kidney, and brain occurred significantly above expectation, and the occurrence of malignant lymphomas was below expectation. SIR for all cancers combined among patients with Graves' disease surviving 10 years or more was 1.03 (95% CI = 0.93-1.12; n = 457); among patients with toxic nodular goiter, it was 1.21 (95% CI = 1.08-1.35; n = 314). None of the site-specific SIRS following Graves' disease differed significantly from unity. Significantly elevated SIRS were observed following toxic nodular goiter for stomach cancer (SIR = 1.95; n = 29), cancer of female genital organs (SIR = 1.42; n = 42), kidney cancer (SIR= 1.81; n = 15), and brain tumors (SIR = 2.21; n = 14).

Among 10-year survivors, SIR for all cancers combined was 1.06 (95% CI = 0.94-1.19) for patients receiving less than 221 MBq of ^{131}I, 1.14 (95% CI = 1.01-1.26) for those receiving 221-480 MBq, and 1.10 (95% CI = 0.96-1.25) for those receiving more than 480 MBq.

Table 4 shows the SIRS for some cancers in relation to the years of follow-up. Except for stomach cancer, there was no significant time trend for any of the cancer sites or for all cancers combined. Interestingly, among 10-year survivors, the risk for stomach cancer increased with dose, from an SIR of 0.99 among patients receiving less than 221 MBq to an SIR of 1.64 among those receiving more than 480 MBq; this trend, however, was not statistically significant. Assuming a dose of 0.25 Gy to the stomach, a relative risk (RR) at 1 Gy can be estimated as 2.32 and an absolute risk as 9.6 x 10^{-4} PY Gy^{-1}.

Discussion

Patients who received ^{131}I therapy for hyperthyroidism had an overall cancer risk only slightly greater (6%) than that expected in the general population. The risk was somewhat higher among patients with toxic nodular goiter than among patients with Graves' disease. When cancer risk was evaluated in relation to administered dose of ^{131}I, there was no obvious dose-response pattern. Except for stomach cancer the risk did not increase with time since ^{131}I exposure for any individual site or for all sites combined.

This study population represents a selected group because those patients who did not qualify for surgery received either ^{131}I

Table 2. Observed No. of cancers and SIR with 95% Cl in patients with Graves' disease and toxic nodular goiter 1 year or more after therapy*

Cancer site or type	Graves' disease†			Toxic nodular goiter‡		
	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI
Oral cavity, pharynx	9	0.78	0.36-1.48	7	0.87	0.35-1.78
Salivary glands	2	1.02	0.13-3.67	1	1.44	0.02-3.87
Stomach	41	0.87	0.63-1.18	47	1.35	0.99-1.79
Liver	8	0.87	0.38-1.71	15	2.14	1.20-3.52
Pancreas	31	1.05	0.72-1.49	28	1.21	0.81-1.75
Colon, rectum	104	1.04	0.84-1.25	88	1.12	0.90-1.38
Lung	53	1.13	0.84-1.47	45	1.53	1.11-2.04
Female breast	131	0.97	0.81-1.15	126	1.12	0.93-1.33
Female genital organs	90	0.95	0.76-1.16	85	1.12	0.90-1.39
Male genital organs	50	1.02	0.76-1.34	22	0.98	0.61-1.48
Kidney	30	1.17	0.79-1.66	28	1.48	0.99-2.14
Bladder	32	1.26	0.86-1.77	15	0.88	0.49-1.45
Brain	18	0.90	0.53-1.41	28	1.92	1.28-2.78
Thyroid gland	6	0.81	0.30-1.76	10	1.74	0.84-3.20
Parathyroid gland	14	1.60	0.88-2.68	13	1.82	0.97-3.11
Lymphomas	14	0.67	0.37-1.12	13	0.48	0.26-0.81
Multiple myeloma	8	0.75	0.33-1.48	12	0.87	0.45-1.51
Leukemias	14	0.99	0.54-1.66	19	0.78	0.47-1.21
All cancer sites and types§	761	0.99	0.91-1.05	684	1.12	1.04-1.21

*Excludes patients for whom no information on type of disease is available
†Person-years = 77583.
‡Person-years = 52621.
§Includes sites and cancer types not listed in table.

Table 3. Observed No. of cancers and SIR with 95% CI in patients treated with ^{131}I for hyperthyroidism at 10 years or more of follow-up*

Cancer site or type	No. of cancers	SIR	95% CI
Oral cavity, pharynx	13	1.23	0.66-2.10
Salivary glands	2	1.15	0.14-4.13
Stomach	58	1.33	1.01-1.71
Liver	12	1.19	0.62-2.08
Pancreas	36	1.17	0.82-1.62
Colon, rectum	121	1.17	0.97-1.39
Lung	50	1.17	0.87-1.54
Female breast	134	1.03	0.86-1.22
Female genital organs	89	1.08	0.87-1.33
Male genital organs	46	1.02	0.75-1.36
Kidney	37	1.51	1.06-2.08
Bladder	28	1.13	0.75-1.63
Brain	30	1.63	1.10-2.32
Thyroid gland	9	1.32	0.61-2.50
Parathyroid gland	15	1.60	0.90-2.63
Lymphomas	11	0.53	0.27-0.95
Hodgkin's disease	4	1.21	0.33-3.09
Non-Hodgkin's lymphomas	7	0.40	0.16-0.82
Multiple myeloma	10	0.93	0.45-1.71
Leukemias	20	1.07	0.65-1.64
All cancer sites and types†	830	1.10	1.02-1.17

*Person-years = 60038.
†Includes cancer sites and types not listed in table.

or thyrostatic medication. Young patients and women of childbearing age were less likely to receive ^{131}I. This selection bias could possibly influence the risk.

Radiation doses to organs other than the thyroid were generally well below 50 cGy. The stomach received the highest dose, and the risk for stomach cancer among 10-year survivors was significantly elevated. Furthermore, the risk was seen to increase with time since exposure and with the dose of ^{131}I administered. There was no increased risk for cancer of the bladder, however, which received almost as large a dose as the stomach. Elevated risks for these two sites have been observed at higher doses among atomic bomb survivors *(9)* and among women given radiotherapy for cervical cancer *(10)*, as well as among patients with thyroid cancer given much higher doses of ^{131}I than patients with hyperthyroidism *(8)*. One previous study of patients treated for hyperthyroidism with ^{131}I did not reveal a stomach cancer excess *(4)*.

Although many multiple comparisons were made and the fact that the dose to the stomach was high (on average 25 cGy), the increasing trends with time and dose suggest that radiation might partially explain the excess. The RR estimate of 2.32 at a dose of 1 Gy is comparable with estimates from studies of atomic bomb survivors *(9)* and cervical cancer patients *(10)*. Other studies might look to confirm this observation.

There is renewed interest in the possibility that low-dose radiation might result in detectable increases in leukemia among prenatally exposed children, occupational groups, and persons residing in areas of real or supposed increased levels of radiation *(11,12)*. On the basis of studies of atomic bomb survivors and on uncertain extrapolation from much higher dose levels, a dose to the active bone marrow of about 6 cGy of ^{131}I would be expected to result in an RR of approximately 1.30 *(9)*. In actuality, we observed a lower than expected risk (SIR = 0.94; 95% CI = 0.65-1.31). Because leukemia is the most frequently observed radiation effect, in large part due to its early onset after exposure and the apparently high sensitivity of the bone marrow, the absence of any increase in leukemia in our series is noteworthy. A previous large-scale study also failed to identify an increased risk of leukemia following ^{131}I therapy for hyperthyroidism *(1)*. These observations suggest that *(a)* low doses of radiation are less effective carcinogens than high doses, *(b)* the protracted nature of the ^{131}I exposure (physical half-life = 8 days) results in more opportunity for cellular repair of radiation damage than is possible when exposures are received over a short time, or *(c)* the dose was so low that a detectable increase in leukemia was unlikely in our study.

Female breast tissue is especially sensitive to radiation carcinogenesis *(13)*, and an increased risk of breast cancer following ^{131}I therapy for hyperthyroidism was suggested in one series *(6)* but not in others *(5,14)*. Data from studies done on atomic bomb survivors revealed an increased risk for breast cancer, but

Table 4. Observed No. of cancers and SIR with 95% CI in patients treated with ^{131}I for hyperthyroidism in relation to duration of follow-up for selected cancers

	Years of follow-up*											
	1-4 (PY = 35 949)			5-9 (PY = 43 031)			10-14 (PY = 31 212)			≥15 (PY = 28 826)		
Cancer site or type	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI
Stomach	16	0.87	0.50-1.41	18	0.70	0.42-1.11	23	1.10	0.70-1.65	35	1.54	1.07-2.14
Liver, gallbladder, bile ducts	9	1.00	0.46-1.89	20	1.33	0.81-2.04	16	1.11	0.64-1.80	17	0.96	0.56-1.54
Pancreas	6	0.61	0.23-1.32	21	1.35	0.84-2.06	20	1.41	0.86-2.17	16	0.97	0.55-1.57
Lung	25	1.73	1.12-2.55	30	1.33	0.90-1.89	20	0.99	0.61-1.53	30	1.33	0.90-1.90
Female breast	67	1.20	0.93-1.52	68	0.88	0.68-1.11	64	1.01	0.78-1.29	70	1.06	0.82-1.33
Kidney	14	1.50	0.82-2.51	15	1.10	0.62-1.80	23	1.95	1.24-2.93	14	1.10	0.60-1.83
Bladder	7	0.87	0.35-1.79	16	1.26	0.73-2.05	14	1.22	0.67-2.05	14	1.05	0.58-1.76
Brain	8	0.93	0.40-1.82	10	0.86	0.41-1.57	17	1.74	1.02-2.78	13	1.30	0.69-2.21
Thyroid gland	4	1.33	0.36-3.39	5	1.20	0.39-2.80	5	1.49	0.49-3.48	4	1.15	0.32-2.94
Parathyroid gland	8	2.88	1.25-5.68	7	1.49	0.60-3.06	4	1.19	0.33-3.04	11	1.83	0.92-3.27
Leukemias	8	1.14	0.50-2.25	6	0.58	0.22-1.26	8	0.89	0.39-1.76	12	1.19	0.62-2.08
All cancer sites and types†	317	1.12	0.99-1.24	396	0.96	0.86-1.05	394	1.10	0.99-1.21	436	1.10	1.00-1.20

*PY = person-years.
†Includes cancer sites and types not listed in table.

only among patients exposed under the age of 40 *(9)*. These findings were confirmed by Hoffman and McConahey *(15)*. Our study found no elevation in breast cancer risk (SIR = 1.02) based on 269 cancers. However, the estimated average dose of 6 cGy to the breast was so low that a detectable increase in breast cancer would not be expected even in a sample of this size.

Therapeutic x irradiation with doses as high as 60 Gy in childhood has been linked to significant risks of thyroid cancer *(16,17)*. Only a small and nonsignificant increase (SIR= 1.29; n = 18) was observed in our study; this increase occurred only among patients with toxic nodular goiter. The much higher radiation doses from internal ^{131}I than from external x rays results in substantially more cell killing, which might explain these different results. The adult gland might also be substantially less susceptible to radiation carcinogenesis than the gland of a child.

Multiple myeloma was not increased (SIR = 1.05; n = 21), contrary to some, but not all, radiation studies *(9,10,18)*. Lymphomas were almost significantly decreased but have been suggested to develop only after therapeutic doses *(10)*. Lung cancer was significantly increased, but only in years 1-4 after exposure. A previous study has reported high risks of respiratory cancer among women with hyperthyroidism apparently not treated with ^{131}I *(14)*.

There is mounting evidence from human studies, similar to animal and cellular experiments *(19,20)*, that doses received gradually over time may be less carcinogenic than the same total dose received by a brief exposure. For example, no risk of thyroid nodularity was found among women residing in areas of high background radiation in China compared with women exposed to lower levels of radiation, despite a difference of dose to the thyroid of 9 cGy *(21)*. No increased risk of thyroid cancer in 35000 patients given diagnostic doses of ^{131}I (mean, 50 cGy) was observed among those followed for 10 or more years *(22)*. Women with tuberculosis given large numbers of chest fluoroscopes were found to be at increased risk for breast cancer, but not lung cancer, despite doses to the lung of the order of 0.8 Gy *(11,23)*. While breast cancer may be a special case for which protracted exposures do not appreciably reduce risk, for many tumors a lessening of risk may accompany such intermittent exposures *(24)*.

Overall, our data on over 10000 patients with hyperthyroidism treated with ^{131}I provide little evidence that relatively low doses of radiation are associated with a detectable increase in cancer in humans. Despite the inherent limitations of studies of populations exposed to low levels of radiation *(11,25)*, our data are reassuring and suggest that risk estimates based on higher dose surveys of brief exposure do not appear to overestimate risks following therapy for hyperthyroidism. If anything, risks at low doses might be lower than predicted from high-dose studies.

The present results should not cause any restrictions as regards the principles for ^{131}I therapy in patients with hyperthyroidism. At present, patients aged 35 years or more are primary candidates for ^{131}I therapy in Swedish hospitals. With the present long-term follow-up, some of us are now contemplating lowering the present age limit. Such a change should, however, be made in small steps so that any possible influence of age at radiotherapy could be detected by follow-up studies,

Some institutions advocate giving standard doses of ^{131}I to the patients, in some cases even without knowledge of whether or not the patients have any thyroid uptake of ^{131}I. Radiotherapy for hyperthyroidism must follow the ALARA principle (i.e., the administered dose should be As Low As Reasonably Achievable) in order to obtain the desired clinical effect. ^{131}I tracer measurements should always be performed, and the ^{131}I dose administered for therapeutic purposes should be based on calculations taking into account the thyroid volume as well as the uptake and effective half-life of ^{131}I in the thyroid gland.

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